

**Non-Technical Abstract:**

Chronic wounds in the skin represent a significant medical problem in millions of people each year, including 800,000 persons with diabetes. Individuals with long-standing diabetes have poor circulation, which results in less oxygen and nutrients going to the extremities (feet), and lose their sense of touch and pain in their feet. Thus, they may not feel pressure from shoes or objects which can damage their skin. Once a wound is formed, it may heal very slowly, or not at all, due to the diabetes and its complications. Treatment includes various dressings that keep the wound clean and moist, keeping weight and pressure off of the wound, and vigorous cleaning of any dead tissue in the wound. Recently, a protein called platelet-derived growth factor-B (PDGF-B) was identified, which is found in normal wounds and is important for healing, but is not found in chronic wounds. This protein, when administered in a gel to the surface of the wound, has been shown to stimulate healing in some persons with chronic diabetic ulcers. A number of individuals, however, responded poorly, largely because the PDGF-B does not stay within the wound bed very long. It is destroyed or lost quickly, and even when reapplied daily, is not very effective.

To overcome the delivery problem, Tissue Repair Company has used the gene that produces PDGF-B protein. We have placed this gene into a crippled adenovirus, and placed the virus into a collagen matrix having the consistency of toothpaste. This formulated material is termed GAM501 (Gene Activated Matrix). GAM501 has been placed into animal models of wound healing and found to induce large amounts of new granulation (wound repair) tissue, resulting in healed wounds. It remains localized within the wound, where cells migrate in and take up the DNA, and is not toxic. The wound repair cells then make PDGF-B protein within the local environment, which stimulates a cascade of tissue repair activities, leading to a healed wound.

Tissue Repair Company is studying the effects of GAM501, an investigational gene therapy product, in subjects with non-healing diabetic ulcers of the lower extremities. The purpose of this study is to test the effects (good and bad) of GAM501 and whether or not it will facilitate the repair process in individuals with chronic diabetic ulcers.

GAM501 has been evaluated in a Phase I study in 15 subjects with non-healing ulcers of the lower extremities. GAM501 was well tolerated and did not appear to cause abnormalities in hematology, chemistry and urinalysis values. Most of the subjects had a positive clinical response to GAM501 with 67% achieving ulcer closure.